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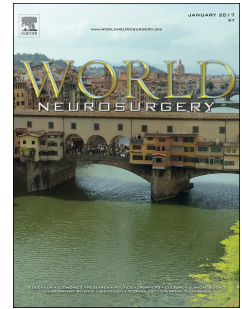
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First UK experience of navigated Transcranial Magnetic Stimulation in pre-surgical mapping of brain tumours

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Running title: 1st UK experience of nTMS in pre-surgical mapping

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First UK experience of navigated Transcranial Magnetic Stimulation in pre-surgical mapping of brain tumours

Introduction

Surgery for lesions in eloquent brain areas remains challenging due to the risk of causing a permanent neurological deficit. Direct Electrical Stimulation (DES) at cortical and subcortical level represents the "gold standard" in minimising these risks.¹⁻⁶ More recently, navigated Transcranial Magnetic Stimulation (nTMS) has emerged as a non-invasive mapping tool assisting neurosurgeons in optimising surgical planning for lesions in eloquent brain.⁷⁻¹¹ Using a high-precision coil, matched with neuronavigation and analytic software, it delivers biphasic magnetic stimulation to the cortex.¹² Its main application has been motor and language mapping. Single pulse nTMS, applied to the primary motor cortex (PMC), generates muscle output which is recorded via a continuously running electromyogram.¹²

Upon application of repetitive nTMS to the cortex, a transient disruption of areas responsible for language processing and execution occurs.¹³ Depending on location within the brain and type of surgery, pre-operative nTMS can therefore elucidate the perilesional functional cortical organisation. Although previous studies have focused on the role of nTMS compared to DES, more data are required to further validate this technique. In addition, a previous study suggested the utility of nTMS in refining and modifying the surgical approach to lesions in eloquent areas.¹² These findings, although encouraging, have not been independently reassessed or replicated.

We report the first UK experience in the use of nTMS, correlating our TMS results with the intra-operative findings and assessing its impact on surgical decision-making.

Methods and materials:

Patients

We retrospectively reviewed patients undergoing craniotomy for removal of brain tumour at our institution with pre-operative nTMS, intra-operative neuromonitoring (IOM) and DES between February 2017 and February 2018.

Inclusion criteria were: age ≥ 18 years, brain tumour involving motor or language eloquent area (assessed by anatomical location on structural Magnetic Resonance Imaging (MRI) and/or clinical presentation) and Performance status <2 on the Zubrod scale.¹⁴

Ethical Standard

The use of nTMS pre-operatively has been approved by our institution's Neurosciences Research Advisory Group. Patients provided written consent to undergo nTMS in addition to the standard of care.

Pre-operative imaging

All patients underwent pre-operative high-resolution brain volumetric MRI (1.5 Tesla; slice thickness ≤ 1 mm; Siemens Healthcare GmbH, Germany) including a T1 sequence with gadolinium contrast used for nTMS as well as intra-operative neuronavigation.

Pre-operative nTMS

For pre-operative mapping the eXimia Navigated Brain Stimulation System (NBS, Nexstim, Helsinki, Finland) was used with pulse delivery from a figure-of-eight coil.³ It calculates the strength, location, and direction of the stimulating electric field into cortical tissue.¹⁵ Estimates of the induced electric field are based on a dynamic spherical model adjusted in real time and on physical stimulation parameters.^{16,17}

Both hemispheres were examined for motor and language assessment, as previously described by Picht et al.^{3,18} The Resting Motor Threshold (RMT), defined as the lowest stimulation intensity capable of eliciting motor evoked potentials (MEPs) was identified using the adaptive method in both hemispheres for the hand and leg area. At each nTMS trial, the model recalculates an intensity that yields a 50% probability of evoking a MEP which is then selected for the next TMS pulse.¹⁹ The TMS hotspot was demarcated as the stimulation position eliciting the strongest MEP at 105% RMT. MEPs were systematically recorded from: abductor pollicis brevis (APB), first digital interosseous (FDI) and abductor digiti minimi (ADM) for the hand; tibialis anterior (TA) and abductor hallucis brevis (AHB) for the lower limb.

Speech mapping was performed using the NEXSPEECH model (Nexstim Oy, Helsinki, Finland). Two baseline recordings of naming objects were performed with 700 ms picture presentation time and 2500 ms inter-picture interval (or 3000 ms, according to patient's ability). Repetitive nTMS was then applied at RMT with the patient performing the object naming task, and delivered in 5 Hz/5 pulses trains with 0 ms delay. Naming errors were divided into: no responses, performance errors (slurred, imprecisely articulated, stuttered), hesitations, semantic and phonological paraphasias.^{20,21} A limitation of this protocol is the inability to distinguish between anomia and speech arrest as no lead-in phrase ("this is a") is used during this technique. Another dissimilarity to language mapping with DES is that all naming errors (single, repetitive) were included in the final nTMS language map.

Intra-operative DES mapping

Intra-operative motor mapping was performed using a train of 5 stimulation with 0.5 ms pulse width and 2 ms duration, using a constant current stimulator and a monopolar probe

(ISIS Xpress System, Inomed GmbH). Stimulation was anodal at cortical level and cathodal at subcortical level. The stimulation intensity was increased in 1 mA steps until MEPs were obtained. Motor responses were recorded from face, upper limb/hand and lower limb/foot according to tumour location and extent of motor cortex exposure. After defining the motor cortex with brain stimulation, a 4-contact subdural strip electrode was placed over the precentral gyrus eliciting continuous MEPs to monitor the integrity of the corticospinal tract.^{22,23}

Language mapping was performed according to the “Penfield technique”²⁴ using a bipolar probe (2 mm diameter ball tips spaced 5 mm apart, Inomed GmbH). Biphasic square wave pulses of 1 ms duration were applied at 50 Hz using a constant current stimulator (ISIS Neurostimulator, Inomed GmbH). The current threshold during DES was set at the minimum current capable of inducing a speech arrest during a counting task, at least 2 out of 3 times, , starting at 2 mA and increasing until errors were elicited or after discharges observed in the electrocorticography. The site of stimulation was at the level of the ventral premotor cortex or the inferior frontal gyrus (pars opercularis).²⁵

Intra-operative testing was performed by a Speech Therapist with counting, object and verb naming tests. All positive sites were tag-marked and photographed with a high-resolution camera or microscope (Carl Zeiss Microscopy GmbH, Germany). The patient was kept awake during subcortical resection for continuous language mapping and re-anaesthetised once considered safe.

Tumour removal was performed with the aim of maximal resection according to anatomical and functional boundaries. More specifically, in the low grade gliomas (LGG), the surgical endpoint was defined as reaching anatomical and/or functional boundaries in all cases. This

was particularly the case at the subcortical level, when the resection was stopped when positive responses were obtained with subcortical stimulation. In the high grade glioma (HGG) patients, the resection was intended to remove the contrast-enhancing component of the tumour, and it was aided by the use of 5-ALA (Gliolan[®], medac, Gesellschaft für klinische Spezialpräparate mbH, Germany). Therefore, the tumour resection was stopped (again particularly at subcortical level) when either no residual fluorescence was observed, or when functional boundaries were reached.

Comparison between intra-operative DES and pre-operative nTMS

Neuronavigation (StealthStation[®], S7 Surgical Navigation System, Medtronic) was used in all cases to select the approach and to confirm the sites of stimulation over the motor cortex. The high-definition photographs of positive stimulation sites collected during intra-operative mapping were then included in the pre-operative MRI (T1-weighted images post-gadolinium injection) by comparing the anatomical landmarks (i.e. sulci and gyri) of the single pictures with the axial brain volumetric images and reformatted sagittal/coronal images orientated according to the patient's intra-operative head positioning.^{26,27} In 9 cases sufficient exposure of the PMC allowed for complete mapping of the hand knob including intra-operative assessment of the APB hotspot. This was correlated with the TMS map by creation of a visual overlay. Mean distance \pm SEM between the DES and nTMS APB hotspots was calculated.

For language mapping, positive intra-operative sites were correlated with nTMS mapping using the Corina parcellation system.²⁰ allowing for calculation of Specificity, Sensitivity, Positive and Negative Predictive Values (PPV, NPV).

Change of surgical approach

The integration of the nTMS data into surgical planning was independently assessed by two fully qualified neurosurgeons (A.G./F.V.). The surgeon was faced with clinical presentation, neurological symptoms, and pre-operative MR images to formulate the initial surgical plan. Then, nTMS mapping data were reviewed. The influence was classified using a descriptive categorization scale (adapted from Frey et al.): (0) no change; (ia) modification of surgical access pathway; (ib) modification of craniotomy size; (ii) change in planned extent of resection (EoR); (iii) change in surgical indication.¹²

Extent of tumour resection

The EoR in Gliomas was independently assessed by two Neuroradiologists comparing pre- and post-operative MRI (≤ 72 hours). In LGG the extent of Fluid-attenuated inversion recovery (FLAIR) signal was used to assess resection, while in HGG the extent of contrast enhancement on T1-weighted images was used, respectively. EoR was classified according to Berger et al.: “Gross Total Resection” (GTR; no residual), “Subtotal Resection” (STR; residual volume ≤ 10 ml), “Partial Resection” (PR; >10 ml residue).²⁸

Post-operative assessment of neurological function

We prospectively gathered data on neurological outcome. In our department, patients are routinely neurologically assessed after awaking from surgery followed by daily assessments until hospital discharge. New post-surgical neurological deficits were categorized as either a permanent deficit (defined as a new/aggravated paresis or dysphasia >6 months) or a transient deficit (new/aggravated paresis or dysphasia for ≤ 6 months).

Data analysis

Descriptive statistics were used to characterize the patient population. Statistical analysis was performed using GraphPad Prism V7. Chi square and Mann-Whitney U test were used to analyse similarity between motor or speech mapping patient cohorts.

Results

Patients

24 patients (68.6%) underwent pre-operative nTMS mapping for motor function and 11 patients (31.4%) for language (*Table 1*) with a mean age of 47 years with equal M:F ratio in both groups. Right hand dominance was naturally distributed (91.4%).^{28,30}

Motor mapping was performed most commonly for lesions in the parietal lobe (n=7) or central lobule (n=7) and speech mapping for lesions in the frontal (n=4) or temporal (n=4) lobes. 88.6% of patients had a Glioma (n=24 HGG; n=7 LGG). Other histological diagnoses included metastasis (n=2), epidermoid cyst (n=1) and cavernoma (n=1).

Post-operative infection (n=5) was the most common complication, followed by seizures (n=3). One patient had a conservatively managed small post-operative haemorrhage. No mortality was observed in this series.

13 patients suffered a new post-operative neurological deficit (37.1%) which was transient in n=11 (31.4%). One patient's left-sided weakness improved immediately after surgery, but a longstanding foot weakness worsened from BMRC 2/5 to 1/5 in dorsiflexion, requiring a walking stick.

One patient suffered a permanent expressive dysphasia. This was a case of a patient with a WHO grade III anaplastic oligodendroglioma invading the left frontal lobe, mainly the left

Supplementary Motor Area (SMA). Pre-operative nTMS had been negative for language and no DES positive language sites were injured during surgery. The patient developed immediate post-operative mutism, consistent with SMA syndrome, which initially improved post-operatively. Unfortunately this recovery was set back when the patient developed a post-operative infection with brain abscess, requiring surgery for bone flap removal and abscess drainage. It remains difficult to ascertain how much these factors played a role in the development of a long-lasting speech problem.

Correlation between pre-operative TMS and intra-operative motor mapping with DES/IOM

Out of 24 patients, we were able to identify the hand knob and leg/foot area in 23 cases during pre-surgical mapping with nTMS. The one patient where nTMS could not identify the hand and leg areas had a large left frontotemporal pilocytic astrocytoma associated with a longstanding, severe pre-operative right-sided weakness, which was more severe distally (hand and foot BMRC 0/5). nTMS was unable to elicit MEPs from the motor cortex relatively to the mapped muscles. Intra-operative DES was able to pick up small MEPs, mainly from the proximal upper limb muscles, which remained stable throughout the procedure. The patient stayed neurologically unchanged post-operatively.

The PMC was exposed and mapped with DES in 11 patients. The hand knob was identified in all 11 cases. The foot area was exposed and mapped in 4 cases. In 13 patients nTMS was used to guide strip electrode positioning onto the unexposed PMC. In the 11 cases with full mapping of the hand knob area, nTMS and DES hotspots were located on the same gyrus. This is demonstrated in *Figure 1A*, showing the snapshot hotspot conformity between nTMS and the intra-operatively mapped hand knob as identified by DES (n=9) for APB muscle with a mean distance of $3.50 \text{ mm} \pm 0.66 \text{ mm}$ (*Figure 1B*).

Correlation between pre-operative TMS and intra-operative language mapping

While in most cases motor hand function was found both with nTMS and DES within the radiologically defined “hand knob” of the primary motor cortex,³¹ speech areas were more widely distributed, and tended to cluster along perisylvian regions, making a correlation between anatomical landmarks and TMS/DES less predictable.³²

We were able to identify positive language sites (*Figure 2A*) with nTMS in 9/11 patients (81.8%). One patient had to be excluded from analysis (*Figure 2C*) as no intra-operative mapping with DES could be performed due to an intra-operative seizure. This was a patient with a left frontal LGG involving the middle and superior frontal gyri where nTMS language mapping had identified language to be located in vPoG and aSTG anatomical regions, therefore away from the location of the tumour. After a seizure occurred during the initial stimulation intra-operatively, awake surgery was abandoned and tumour debulking was performed based on anatomical landmarks. In particular, the inferior frontal gyrus and ventral premotor cortex were spared. The patient woke up without any language deficits.

We obtained True-positive (TP) responses (definition *Figure 2B*) in 7 patients distributed across 4 different language regions (vPrG, vPoG, aSMG, pSMG). When looking at the types of errors induced, there seems to be a good correlation between hesitation and phonological errors between nTMS and DES. Performance errors during nTMS (slurred speech, stuttering, etc.) may be correlated with intra-operative speech arrest, however this was done in a small patient cohort.

True-negative (TN) responses were evenly distributed. False-positive (FP) responses were present in 5 patients and more evenly distributed (opIFG, mMFG, aSMG, pSTG, pSMG, mPrG). There were only 7 False-negative (FN) responses overall.

Sensitivity of nTMS was 63.2% with a PPV of 54.5% (*Figure 2D*). NPV was 74.1% with a Specificity of 66.7%. 5/11 patients suffered from post-operative transient dysphasia and one patient had permanent expressive dysphasia.

Extent of Resection (Gliomas only)

The radiological EoR was assessed within the Glioma subgroup where postoperative MRI ≤ 72 hours was available (n=23; 74.2%).

Within the HGG group (n=16), GTR (n=12) was achieved in 75.0% and STR in 25.0% (n=4). Within the LGG subgroup (n=7), STR was performed in the majority of cases (71.4%, n=5). One case underwent GTR (14.3%) and in one case only PR was deemed possible.

Change of Surgical Approach

The use of pre-operative nTMS for language mapping or motor mapping changed surgical planning in 28.6% (n=10, *Table 2*). This modification was either a change in access pathway (n=3, 8.6%) or a change in craniotomy size, favouring a smaller craniotomy, in n=7 (20.0%). The surgical indication was changed from no surgery to resection in one patient (2.9% of total). This was a case of a cavernoma where prior to nTMS mapping, surgery had been deemed too risky due to its location suggestive of motor area involvement.

Discussion

Role of TMS in neurosurgery

Although DES combined with IOM remains the “gold standard” for surgery in eloquent brain,³²⁻³⁶ different modalities have been developed to assist in pre-operative planning. This is important - both, to obtain a risk estimate helping the process of informed consent, and to aid in planning the surgical strategy before entering the operating room.

Functional MRI (fMRI), employing blood-oxygen-level dependent (BOLD) technique as a metabolic surrogate of function, has been used to assess the functional arrangements of areas involved in movement and language.³⁷⁻³⁹ However, fMRI (Sensitivity 59%-100%, Specificity 0-97% compared to DES in language mapping)⁴⁰ is heavily operator dependent in terms of image acquisition and processing. In addition, diffusion-based tractography has been developed to study white matter connections of the brain *in vivo* but is limited by lack of functional information.⁴¹⁻⁴³ TMS, initially described in 1985 by Barker et al., has emerged over the last decade as an additional mapping tool directly assessing physiology and function.⁴⁴ Several studies described the safety, reliability and efficacy of the method^{8-10,45,46} and argued on improved pre-operative planning, risk stratification^{7,47} and patient counselling.⁴⁸ From a practical point of view, whilst task-based fMRI relies on resources within the neuroradiology department, nTMS is a tool operated by the neurosurgical team using the routinely acquired neuronavigation MRI sequence and can thus be readily integrated into the workflow.

Accuracy and reliability of nTMS for motor mapping

In our experience, nTMS reliably and reproducibly predicted the PMC. Except for one case with severe pre-operative motor deficit, we were able to identify the hand knob and leg/foot area in all patients. Neither FPs nor FNs were identified with DES/IOM.

Takahashi et al. have validated TMS accuracy to be ± 5.6 mm away from the DES hotspot⁴⁹ and this was confirmed similarly by other studies.^{3,12} More specifically, Picht et al. showed a mean distance of 4.70 ± 1.09 mm between APB hotspot (n=8) in nTMS and DES,³ which in their experience was more accurate than TA hotspots. In our patient cohort we observed mean accuracy of $3.50 \text{ mm} \pm 0.66 \text{ mm}$ for APB (n=9). Although we have not demonstrated a mean distance for the foot/leg area due to small case number, the nTMS findings have been

accurate compared to DES. Our experience therefore supports nTMS as being precise and reliable in predicting location of hand knob and foot/leg area on the PMC. In our experience, it may also shorten the length of surgery two-fold: Firstly, the pre-operative functional mapping with nTMS can help in guiding the intra-operative stimulation, thus reducing the time spent to obtain a cortical mapping. In addition to that nTMS was able to change the craniotomy size (opting for a smaller craniotomy) in a substantial amount of patients. Performing a more targeted craniotomy, which means having a shorter surgical incision, smaller dural opening, etc., may also help in reducing the overall duration of the surgical procedure, particularly shortening the opening/closing times.

Role of nTMS in pre-operative language mapping

nTMS language mapping is a well-tolerated procedure (n=2 in our series reported discomfort of temporalis muscle). Previous studies evaluated the Sensitivity and Specificity of nTMS in language mapping.^{11,18,50,51} Picht et al. assessed nTMS and DES responses in 20 patients with tumours close to left-sided language areas.¹⁸ Their findings showed a Sensitivity of 90.2%, Specificity of 23.8%, PPV of 35.6%, and NPV of 83.9%. NPV was higher (100.0%) when looking at Broca's area only. A subsequent study by Tarapore et al. also demonstrated a high NPV (99.0%) with improved Specificity (98.0%) in a smaller cohort of patients.¹¹

Our results compare favourably with previously published data in terms of Sensitivity and Specificity and demonstrate that nTMS has a particularly high NPV. In fact Ille et al. suggested that resection of language eloquent lesions may be safe based solely on pre-operative language findings in patients not suitable for awake surgery.⁵² However, language mapping with nTMS still has limitations. As previously reported,⁵³ negative mapping can occur with nTMS (n=2 in our series). In addition, FP language sites are common, making

nTMS less reliable in terms of PPV. To overcome these limitations, some studies have looked at different stimulation parameters to improve reliability of language mapping.¹¹ In particular, Krieg et al. found that better PPV results can be obtained with 0 ms stimulus delay.⁵⁴ Other groups have looked into alternative language tests, such as action naming and verb generation.⁵⁵⁻⁵⁷

Change of approach and clinical outcome

The impact of nTMS in surgical planning has been previously evaluated by Frey et al. In their series, nTMS showed a net change from no surgery or biopsy to open surgery of 68.5% (37/54).¹² In our series, the approach to surgery was influenced by nTMS in 12/35 cases (34.3%). When the size of craniotomy was affected, we opted for a smaller craniotomy as we were able to anticipate the location of motor areas. In these cases, nTMS guided the subdural strip electrode placement without exposing the PMC. In three cases the surgical strategy for tumour access was modified, which in two cases was due to the location of the PMC relative to the tumour. In the case of a left insular glioblastoma, nTMS showed a negative language mapping over the left frontal operculum (*Figure 3*) leading to a trans-opercular approach.

Lastly, nTMS disproved involvement of the PMC in the case of a cavernoma thereby altering the initial decision not to operate due to the perceived high risk of surgery. The role of nTMS in optimising surgical planning has been previously related to an improved treatment outcome for patients with brain tumours.^{12,47,58}

nTMS potentially influences post-operative neurological deficits, as it has been described in the risk stratification model by Rosenstock et al.⁷ Furthermore, in surgical series where nTMS was used additionally to DES, higher rates of transient neurological deficits have been

reported. This could be due to increase in surgical indications and aim for GTR for tumours in eloquent areas.⁴⁸ In our cohort, 11/35 patients (31.4%) suffered transient deficits and only two patients had a permanent deficit. One patient with long term expressive dysphasia also suffered from a post-operative brain abscess requiring surgical evacuation which may have contributed to his neurological sequelae. The second patient, although significantly recovered from transient left-sided weakness remained with a slightly worse foot drop.

Finally, nTMS has had no direct influence on the planned EoR within our cohort. However, other studies have suggested that combination of nTMS with DES/IOM significantly increases EoR⁴⁷ as well as improves progression-free survival of LGG patients.^{12,58} This needs to be further investigated, ideally in a randomised-controlled trial.

The focus of this study was our experience with nTMS as a diagnostic tool, as the first centre in the UK to employ this technique. The next step will be to combine structural connections of white matter tracts with functional assessment acquired with nTMS, therefore adding a further level of information when planning surgery for tumours in eloquent areas.

Conclusions

nTMS is a safe, non-invasive adjunctive tool for pre-surgical mapping of SOL in eloquent areas. It reliably identified the PMC in our cohort with an accurate APB hotspot compared to the “gold standard” DES. Our pre-operative language mapping with nTMS confirmed a high NPV (74.1%) with a Specificity of 66.7%.

Furthermore, nTMS influenced the surgical decision-making in up to 1/3 of patients in our experience.

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Figure legends**Figure 1: Motor mapping**

(A) Correspondence of nTMS with intraoperative DES hotspots for APB (n=9); (B) Mean distance (red bar) in mm for nTMS and DES hotspots (n=9)

Figure 2: Language mapping

(A) Corina parcellation system with nTMS true positive (green) and false positive (red) language sites; (B) Classification of nTMS language mapping results; (C) Details of pre-operative nTMS and intra-operative DES speech mapping results (n=10); (D) Calculated Receiver-operating characteristics (Sensitivity, Specificity, PPV and NPV)

Figure 3: Illustrative case (Patient F) where nTMS led to a change in the surgical approach

This case is a 60 year-old female patient presenting with generalized tonic-clonic seizures and a right-sided facial droop. Imaging revealed a left frontal HGG. The patient underwent pre-operative nTMS language and motor mapping (A) which demonstrated that the language eloquent areas are not located at the tumour site. This led to the decision to approach the tumour via a transopercular approach. The intra-operative DES mapping confirmed our nTMS results (B) with the site of speech arrest being located posteriorly to the tumour. We achieved a GTR which was confirmed by comparing the axial (C)/coronal (D) pre-operative MRI T1-weighted images with contrast to the post-operative MRI (E/F). This patient suffered no post-operative language deficit. She was diagnosed with an unmethylated IDH-1 wildtype Glioblastoma, and has completed the Stupp-regime.

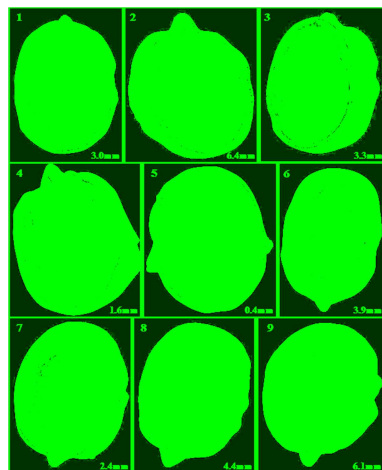
Table 1: Patient demographics, tumour characteristics, complications and neurological outcome

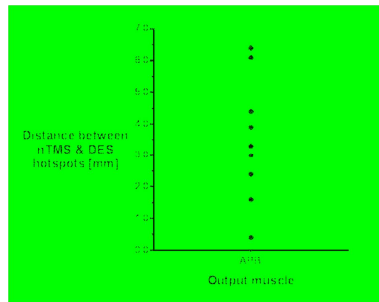
Variables	<i>n</i> TMS N=35 (%)	<i>Motor</i> N=24	<i>Speech</i> N=11	<i>p-value</i>
Gender				p>.05
- Female	18 (51.4)	12	6	
- Male	17 (48.6)	12	5	
Handedness				p>.05
- Right-handed	32 (91.4)	21	11	
- Left-handed	3 (8.6)	3	0	
Age [years]				p>.05
- Mean \pm SD	47 \pm 15	45 \pm 15	50 \pm 13	
- Range	19 - 67	19 - 70	29 - 65	
Hemisphere				P<.001
- Left	19 (54.3)	8	11	
- Right	16 (45.7)	16	0	
Tumour location				p>.05
- Frontal	10 (28.6)	6	4	
- Parietal	9 (25.7)	7	2	
- Central lobule	7 (20.0)	7	0	
- Temporal	5 (14.3)	1	4	
- Insula	3 (8.6)	2	1	
- Cingular	1 (2.9)	1	0	
Diagnosis				p>.05
- HGG ^a	24 (68.6)	15	9	
- LGG ^b	7 (20.0)	5	2	
- Metastasis	2 (5.7)	2	0	
- Epidermoid cyst	1 (2.9)	1	0	
- Cavernous haemangioma	1 (2.9)	1	0	
Histopathology				p>.05
- WHO grade I ^c	1 (2.9)	1	0	
- WHO grade II	5 (14.3)	4	1	
- WHO grade III	10 (28.6)	4	6	
- WHO grade IV ^d	16 (45.7)	13	3	
- Other ^e	3 (8.6)	2	1	
Complications				p>.05
- Infection	5 (14.3)	2	3	
- Seizure	3 (8.6)	2	1	
- Haemorrhage	1 (2.9)	0	1	
New neurological deficit				p>.05
- Transient	11 (31.4)	7	4	
- Permanent	2 (5.7)	1	1	

^a HGG were considered all glioblastoma, anaplastic astrocytoma, and anaplastic oligodendrogliomas^b LGG were considered all other astrocytomas^c WHO grade I tumour includes one ganglioglioma^d WHO grade IV tumours include HGG and 2 metastases^e Other includes one epidermoid cyst, one cavernoma and one LGG not otherwise specified

Table 2: Change of Surgical strategy

Influence of TMS on Surgery	<i>N</i>	% of total
0 No change in surgical plan	24	68.6
i. Modification	10	28.6
a) Change in access pathway	3	8.6
b) Change in craniotomy size	7	20.0
ii. Extent of Resection	-	-
iii. Surgical indication	1	2.9







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Classification	DCS	TMS
True positive	+	+
True negative	-	-
False positive	-	+
False negative	+	-

Patient	DCS			TMS		
A	-	aSMG	-	vPrG*	aSMG	aMFG*
B	vPrG (2x)	-	-	-	-	opIFG
C	vPrG (2x)	-	-	-	-	-
D	vPrG	-	-	vPrG	pSMG*	mMFG anG*
E	vPrG vPoG	-	-	vPrG (2x) vPoG	aSMG*	-
F	vPrG	-	-	vPrG (2x)	aSMG*(2x)	-
G	vPrG	pSMG	-	vPrG	aSMG (2x) pSMG	pSTG
H	vPrG vPoG	-	-	vPrG vPoG	pSMG	-
I	-	-	opIFG	-	-	-
J	vPrG vPoG	-	opIFG	vPrG mPrG	pSMG (2x)	pSTG

DES: Exclusion of one patient where intra-operative mapping was not performed due to seizures.

* Not exposed during surgery.



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	Percentage	Values
Sensitivity	63.2%	TP = 12
Specificity	66.7%	FP = 10
PPV	54.5%	FN = 7
NPV	74.1%	TN = 20

Abbreviation list

Abductor digiti minimi (ADM); Abductor hallucis brevis (AHB); Abductor pollicis brevis (APB); anterior/posterior Supramarginal Gyrus (aSMG/pSMG); Blood-Oxygen level dependent (BOLD); British Medical Research Council (BMRC); Direct Electrical Stimulation (DES); Electrocorticography (ECoG); Extent of Resection (EoR); False Negatives (FN); False Positives (FP); First digital interosseous (FDI); Fluid-attenuated inversion recovery (FLAIR); functional Magnetic Resonance Imaging (fMRI) Gross Total Resection (GTR); High grade glioma (HGG); Inter-picture interval (IPI); Intra-operative neuromonitoring (IOM); Low grade glioma (LGG); Middle middle frontal gyrus (mMFG); Middle Precentral Gyrus (mPrG); Motor evoked potential (MEP); Multidisciplinary Team (MDT); Navigated Brain Stimulation (NBS); navigated Transcranial Magnetic Stimulation (nTMS); Negative Predictive Value (NPV); Not otherwise specified (NOS); Opercular inferior frontal gyrus (opIFG); Partial Resection (PR); Picture presentation time (PPT); Positive Predictive Value (PPV); Posterior superior temporal gyrus (pSTG); Primary Motor Cortex (PMC); Resting Motor Threshold (RMT); Subtotal Resection (STR); Supplementary Motor Area (SMA); Tibialis anterior (TA); True Negatives (TN); True Positives (TP); ventral Precentral/Postcentral Gyrus (vPrG/vPoG); World Health Organisation (WHO)